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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/430,029	10/29/1999	TETSUYA YANO	35.C13982	6685

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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	32

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/430,029	YANO ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- Th MAILING DATE of this communication appears on th cov r sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2* is/are allowed.

6)☒ Claim(s) *1,3-48 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2003 has been entered.

The preliminary amendment filed August 11, 2003 amending claims 3, 6, 9, 10, 13, 17, 22, 28, 34 and 55 has been entered.

Claims 1-48 and 55 are pending.

Claim Objections

Claims 1, 3-48 and 55 are objected to because of the following:
The claims recite "toluene monooxygenase", "toluene monooxygenase protein", "a protein having a toluene monooxygenase activity" and "active toluene monooxygenase" interchangeably. It is suggested that applicants maintain consistency throughout the claims and refer to "toluene monooxygenase", for example.

In claims 1 and 15, last line, a hyphen is not needed between "DNA" and "fragment".

Appropriate correction is required.

Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 recites "no spacer" or "at least one spacer", i.e. both claim 7 and claim 6 comprise sequences with no spacer, one spacer, two spacers, three spacers and four spacers.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-48 and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-48 and 55 recite a "toluene monooxygenase" from any source. The art teaches that there are different toluene monooxygenase activities, including two in

Burkholderia.

The specification teaches only a single toluene monooxygenase from *Burkholderia cepacia* KK01 (formerly, *Pseudomonas cepacia*) that oxidizes toluene to ortho-cresol and 3-methylcatechol in *Burkholderia cepacia* KK01 (page 9, lines 2-13). Moreover, the specification fails to describe representative species of other toluene monooxygenases. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 3, 9, 10, 17 and 55 recite nucleotide sequences/DNA fragments that include "deletion, substitution or addition of one or more bases from cloning". Because the scope of said sequences is not defined (see 112, 2nd paragraph, rejection below), this amounts to any structure having the same function as a protein encoded by SEQ ID NOs: 2-7 or SEQ ID NO:1. This is equivalent to claiming nucleotide sequences with no structural limitations wherein an enzyme or protein is defined by the function only.

The specification discloses no identifying characteristics which would allow to recognize a structure as a member of a gene encoding a toluene monooxygenase activity. Therefore, based on the instant disclosure, it is unpredictable either a protein is a part of a toluene monooxygenase and either a gene is a toluene monooxygenase

gene. Thus, nucleotide sequences/DNA fragments that include "deletion, substitution or addition of one or more bases from cloning, lack sufficient written description needed to practice the instant invention.

Claims 3-14, 17-48 and 55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleotide of SEQ ID NO:1 encoding a toluene monooxygenase that oxidizes toluene to ortho-cresol and 3-methylcatechol comprising SEQ ID NOs: 2-7 and a nucleotide of 234-443 bp of SEQ ID NO: 1 encoding TomK, does not reasonably provide enablement for nucleotide sequences/DNA fragments that include "deletion, substitution or addition of one or more bases from cloning" encoding the toluene monooxygenase or TomK as well as nucleotide sequences/DNA fragments encoding a toluene monooxygenase with different specificity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant invention is directed to a nucleotide encoding a toluene monooxygenase having the sequence different from SEQ ID NO:1 by "deletion, substitution or addition of one or more bases from cloning". The above claims are drawn to sequences having structures different from SEQ ID NO: 1 and the 234-443 portion thereof and encoding a polypeptide retaining the requisite function. Furthermore, SEQ ID NO:1 encodes the specific toluene monooxygenase whereas toluene monooxygenases with other specificities are also known, *supra*.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of a sequence that comprises SEQ ID NO:1 and its portion and encodes the toluene monooxygenase or TomK activity. This is because the specification does **not** establish: (a) regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Despite knowledge in the art to produce mutations in proteins, the specification fails to provide guidance as to where, and what type of (i.e., what amino acid to substitute into, add to or delete from the known sequence), changes in amino acid residues will result in a desired enzymatic activity. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in a certain activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited.

Furthermore, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen large numbers of mutated proteins or genes where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

Therefore, one of ordinary skill in the art would require guidance, in order to make a DNA fragment encoding the toluene monooxygenase or TomK having the sequence other than SEQ ID NO: 1 and its 234-443 portion, respectively, or a toluene monooxygenase with different specificity in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5, 9-14, 17, 18, 21-48 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-5, 9-14, 17, 18, 21-48 and 55 recite nucleotide sequences/DNA fragments that include "deletion, substitution or addition of one or more bases from cloning" (emphasis added). The specification does not define the scope of claims, i.e. how to determine whether a particular deletion, substitution or addition results from cloning or not. Furthermore, the specification does not define the processes that are included in cloning.

Claims 3, 9, 10, 13, 17 and 55 recite "complement" of a nucleotide. A nucleotide can be 100%, or fully, complementary to another nucleotide or while being complementary, contain deletion, substitution or addition of one or more bases. Furthermore, the complement does not, itself, code for the protein in question and its expression would not result in a protein with the requisite activities.

Claim 9 recites nucleotide sequences corresponding to the specific fragments of SEQ ID NO:1 encoding SEQ ID NOs: 3-7 wherein said nucleotide sequences include "deletion, substitution or addition of one or more bases from cloning". It is unclear

whether the scope of the nucleotide sequences is limited to the sequences encoding SEQ ID NOs: 3-7 or not.

Claims 17 and 55 recite "an active toluene monooxygenase". The toluene monooxygenase is presumed active otherwise it is not toluene monooxygenase. Furthermore, other claims do not recite "active" just "toluene monooxygenase".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-5, 9-14, 17, 18, 21-48 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Shields et al.

Shields et al. (US Patent 5,543,317, form PTO-1449 filed April 6, 2000) teach the enzyme having the same function as the enzyme of the instant invention. It is isolated from *Pseudomonas cepacia* $PR1_{23}$, i.e. from another strain of the same species. It is encoded by the nucleotide sequence that is about 70% homologous to SEQ ID NO:1. Thus, the nucleotide sequence of Shields et al. meets the limitation of a sequence having deletion, substitution and/or addition relative to SEQ ID NO:1. They further teach vectors and host cells comprising said sequence and methods of use

thereof. As such, the teachings of Shields et al. anticipate claims 3-5, 9-14, 17, 18, 21-48 and 55.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3-5, 9-14, 17, 18, 21-48 and 55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-19

of U.S. Patent No. 6,472,191 (Yano et al). Although the conflicting claims are not identical, they are not patentably distinct from each other. U.S. Patent No. 6,472,191 teaches a nucleotide from *Ralstonia eutropha* TB64 encoding toluene monooxygenase (SEQ ID NO:1). Nucleotides 108-5411 of SEQ ID NO:1 are about 80% identical to nucleotides 65-5331 of SEQ ID NO:1 of U.S. Patent No. 6,472,191. Thus, SEQ ID NO:1 of U.S. Patent No. 6,472,191 is construed as a sequence having deletion, substitution and/or addition relative to SEQ ID NO:1 of the instant invention. Further, SEQ ID NO:1 of the instant invention will hybridize to SEQ ID NO:1 of U.S. Patent No. 6,472,191 (claims 2-19).

Allowable Subject Matter

Claim 2 is allowed.

Response to Arguments

Applicant's arguments filed August 11, 2003 have been fully considered but they are not persuasive.

Because the undersigned attorney, Michael O'Neill, was not present at the interview conducted on July 28, 2003, the examiner would like to point out inaccuracies in its current coverage. First, the examiner did not suggest that "Applicants refile this application" as stated in Remarks, page 14. Second, the examiner does not agree with

the notion that "variations in a nucleotide sequence are inherent" and could not acknowledge this at the interview (Remarks, page 15, 1st paragraph). The variations may occur. Third, the interview summary was given to the representatives to read before signing by the examiner and they could have requested to include the suggestion to refile, etc. therein.

It is noted, that while Applicants apparently intend to claim highly homologous sequences, the current claims are not limited to said sequences. Furthermore, the current claims are not product by process claims. They are claims drawn to a product the scope of which is not defined.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

October 30, 2003